AUG 2 9 2000

NDA 07-883/S-021, S-027, S-030

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19109-8299

Attention: Jennifer W. Phillips, Pharm.D. Director, Women's Health Care Products
U.S. Regulatory Affairs

Dear Dr. Phillips:

Please refer to your supplemental new drug applications dated October 5, 1983, October 13, 1988, and June 22, 2000, received October 5, 1983, October 17, 1988, and June 23, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Antabuse (disulfiram).

Supplement S-02 1 provides additions to the ADVERSE REACTIONS section of the package insert.

Supplement S-027 provides for minor changes in the INDICATIONS, WARNINGS and ADVERSE REACTIONS sections of the package insert.

Supplement S-030 incorporates safety information regarding the potential for heptatoxicity.

We have completed our review of Supplement S-03 0 and it is approved effective on the date of this letter.

Supplement S-021 and S-027 have been superceded by supplement S-030 and will be retained in the files.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH,HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Antabuse®

(disulfiram)

IN ALCOHOLISM

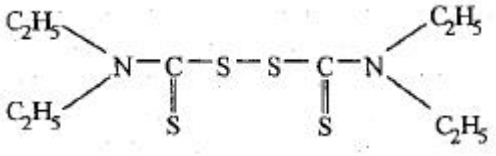
L only

> **WARNING**
>
> Antabuse should *never* be administered to a patient when he is in a state of alcohol intoxication, or without his full knowledge.
> The physician should instruct relatives accordingly.

DESCRIPTION

CHEMICAL NAME: bis(diethylthiocarbamoyl) disulfide

STRUCTURAL FORMULA:



Antabuse occurs as a white to off-white, odorless, and almost tasteless powder, soluble in water to the extent of about 20 mg in 100 mL, and in alcohol to the extent of about 3.8 g in 100 mL.

Antabuse contains these inactive ingredients: magnesium aluminum silicate; magnesium stearate, NF; povidone, USP; starch, NF.

ACTION

Antabuse produces a sensitivity to alcohol which results in a highly unpleasant reaction when the patient under treatment ingests even small amounts of alcohol.

Antabuse blocks the oxidation of alcohol at the acetaldehyde stage. During alcohol metabolism following Antabuse intake, the concentration of acetaldehyde occurring in the blood may be 5- to 10-times higher than that found during metabolism of the same amount of alcohol alone.

Accumulation of acetaldehyde in the blood produces a complex of highly unpleasant symptoms referred to hereinafter as the Antabase-alcohol reaction. This reaction, which is proportional to the dosage of both Antabuse and alcohol, will persist as long as alcohol is being metabolized. Antabuse does not appear to influence the rate of alcohol elimination from the body.

Antabuse is absorbed slowly from the gastrointestinal tract and eliminated slowly from the body. One (or even two) weeks after a patient has taken his last dose of Antabuse, ingestion of alcohol may produce unpleasant symptoms.

Prolonged administration of Antabuse does not produce tolerance; the longer a patient remains on therapy, the more exquisitely sensitive he becomes to alcohol.

INDICATION

Antabuse is an aid in the management of selected chronic alcoholic patients who *want* to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage.

Antabuse is not a cure for alcoholism. When used alone, without proper motivation and supportive therapy, it is unlikely that it will have any substantive effect on the drinking pattern of the chronic alcoholic.

CONTRAINDICATIONS

Patients who are receiving or have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing preparations, e.g., cough syrups, tonics and the like, should not be given Antabuse.

Antabuse is contraindicated in the presence of severe myocardial disease or coronary occlusion, psychoses, and hypersensitivity to disulfiram or to other thiuram derivatives used in pesticides and rubber vulcanization.

WARNINGS

Antabuse should *never* be administered to a patient when he is in a state of alcohol intoxication, or without his full knowledge.
The physician should instruct relatives accordingly.

The patient must be fully informed of the Antabuse-alcohol reaction. He must be strongly cautioned against surreptitious drinking while taking the drug, and he must be fully aware of possible consequences. He should be warned to avoid alcohol in disguised form, i.e., in sauces, vinegars, cough mixtures, and even aftershave lotions and back rubs. He should also be warned that reactions may occur with alcohol up to 14 days after ingesting Antabuse.

The Antabuse-Alcohol Reaction

Antabuse plus alcohol, even small amounts, produces flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death.

The intensity of the reaction varies with each individual but is generally proportional to the amounts of Antabuse and alcohol ingested. Mild reactions may occur in the sensitive individual when the blood alcohol concentration is increased to as little as 5 to 10 mg per 100 mL. Symptoms are fully developed at 50 mg per 100 mL, and unconsciousness usually results when the blood alcohol level reaches 125 to 150 mg.

The duration of the reaction varies from 30 to 60 minutes, to several hours in the more severe cases, or as long as there is alcohol in the blood.

Drug Interactions

Disulfiram appears to decrease the rate at which certain drugs are metabolized and therefore may increase the blood levels and the possibility of clinical toxicity of drugs given concomitantly.

DISULFIRAM SHOULD BE USED WITH CAUTION IN THOSE PATIENTS RECEIVING PHENYTOIN AND ITS CONGENERS, SINCE THE CONCOMITANT ADMINISTRATION OF THESE TWO DRUGS CAN LEAD TO PHENYTOIN INTOXICATION. PRIOR TO ADMINISTERING DISULFIRAM TO A PATIENT ON PHENYTOIN THERAPY, A BASELINE PHENYTOIN SERUM LEVEL SHOULD BE OBTAINED. SUBSEQUENT TO INITIATION OF DISULFIRAM THERAPY, SERUM LEVELS OF PHENYTOIN SHOULD BE DETERMINED ON DIFFERENT DAYS FOR EVIDENCE OF AN INCREASE OR FOR A CONTINUING RISE IN LEVELS. INCREASED PHENYTOIN LEVELS SHOULD BE TREATED WITH APPROPRIATE DOSAGE ADJUSTMENT.

It may be necessary to adjust the dosage of oral anticoagulants upon beginning or stopping disulfiram, since disulfiram may prolong prothrombin time.

Patients taking isoniazid when disulfiram is given should be observed for the appearance of unsteady gait or marked changes in mental status; the disulfiram should be discontinued if such signs appear.

In rats, simultaneous ingestion of disulfiram and nitrite in the diet for 78 weeks has been reported to cause tumors, and it has been suggested that disulfiram may react with nitrites in the rat stomach to form a nitrosamine, which is tumorigenic. Disulfiram alone in the rats' diet did not lead to such tumors. The relevance of this finding to humans is not known at this time.

Concomitant Conditions

Because of the possibility of an accidental Antabuse-alcohol reaction, Antabuse should be used with extreme caution in patients with any of the following conditions: diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis, hepatic cirrhosis or insufficiency.

Usage in Pregnancy

The safe use of this drug in pregnancy has not been established. Therefore, Antabuse should be used during pregnancy only when, in the judgment of the physician, the probable benefits outweigh the possible risks.

PRECAUTIONS

Patients with a history of rubber contact dermatitis should be evaluated for hypersensitivity to thiuram derivatives before receiving Antabuse (see " **CONTRAINDICATIONS** ").

It is suggested that every patient under treatment carry an *Identification Card* , stating that he is receiving Antabuse and describing the symptoms most likely to occur as a result of the Antabuse-alcohol reaction. In addition, this card should indicate the physician or institution to be contacted in an emergency. (Cards may be obtained from Wyeth-Ayerst Laboratories upon request.)

Alcoholism may accompany or be followed by dependence on narcotics or sedatives. Barbiturates and Antabuse have been administered concurrently without untoward effects; the possibility of initiating a new abuse should be considered.

Hepatic toxicity including hepatic failure resulting in transplantation or death have been reported. Severe and sometimes fatal hepatitis associated with disulfiram therapy may develop even after many months of therapy. Hepatic toxicity has occurred in patients with or without prior history of abnormal liver function. Patients should be advised to immediately notify their physician of any early symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, vomiting, jaundice, or dark urine.

Baseline and follow-up transaminase tests (10 to 14 days) are suggested to detect any hepatic dysfunction that may result with Antabuse® therapy. In addition, a complete blood count and a sequential multiple analysis-12 (SMA-12) test should be made every six months.

Patients taking Antabuse Tablets should not be exposed to ethylene dibromide or its vapors. This precaution is based on preliminary results of animal research currently in progress that suggest a toxic interaction between inhaled ethylene dibromide and ingested disulfiram resulting in a higher incidence of tumors and mortality in rats. A correlation between this finding and humans, however, has not been demonstrated.

ADVERSE REACTIONS

(See " **CONTRAINDICATIONS** ," " **WARNINGS** ," and " **PRECAUTIONS** .")

OPTIC NEURITIS, PERIPHERAL NEURITIS, POLYNEURITIS, AND PERIPHERAL NEUROPATHY MAY OCCUR FOLLOWING ADMINISTRATION OF ANTABUSE.

Multiple cases of hepatitis, including both cholestatic and fulminant hepatitis, as well as hepatic failure resulting in transplantation or death, have been reported to be associated with administration of Antabuse.

Occasional skin eruptions are, as a rule, readily controlled by concomitant administration of an antihistaminic drug.

In a small number of patients, a transient mild drowsiness, fatigability, impotence, headache, acneform eruptions, allergic dermatitis, or a metallic or garlic-like aftertaste may be experienced during the first two weeks of therapy. These complaints usually disappear spontaneously with the continuation of therapy, or with reduced dosage.

Psychotic reactions have been noted, attributable in most cases to high dosage, combined toxicity (with metronidazole or isoniazid), or to the unmasking of underlying psychoses in patients stressed by the withdrawal of alcohol.

DOSAGE AND ADMINISTRATION

Antabuse should never be administered until the patient has abstained from alcohol for at least 12 hours.

Initial Dosage Schedule

In the first phase of treatment, a *maximum* of 500 mg daily is given in a single dose for one to two weeks. Although usually taken in the morning, Antabuse may be taken on retiring by patients who experience a sedative effect.

Alternatively, to minimize, or eliminate, the sedative effect, dosage may be adjusted downward.

Maintenance Regimen

The average maintenance dose is 250 mg daily (range, 125 to 500 mg); it should not exceed 500 mg daily.

Note: Occasionally patients, while seemingly on adequate maintenance doses of Antabuse, report that they are able to drink alcoholic beverages with impunity and without any symptomatology. All appearances to the contrary, such patients must be presumed to be disposing of their tablets in some manner without actually taking them. Until such patients have been observed reliably taking their daily Antabuse Tablets (preferably crushed and well mixed with liquid), it cannot be concluded that Antabuse is ineffective.

Duration of Therapy

The daily, uninterrupted administration of Antabuse must be continued until the patient is fully recovered socially and a basis for permanent self-control is established. Depending on the individual patient, maintenance therapy may be required for months, or even years.

Trial with Alcohol

During early experience with Antabuse, it was thought advisable for each patient to have at least one supervised alcohol-drug reaction. More recently, the test reaction has been largely abandoned. Furthermore, such a test reaction should never be administered to a patient over 50 years of age. A clear, detailed, and convincing description of the reaction is felt to be sufficient in most cases.

However, where a test reaction is deemed necessary, the suggested procedure is as follows:

After the first one to two weeks' therapy with 500 mg daily, a drink of 15 mL ($^1/_2$ oz) of 100 proof whiskey, or equivalent, is taken slowly. This test dose of alcoholic beverage may be repeated once only, so that the total dose does not exceed 30 mL (1 oz) of whiskey. Once a reaction develops, no more alcohol should be consumed. Such tests should be carried out only when the patient is hospitalized, or comparable supervision and facilities, including oxygen, are available.

Management Of Antabuse-Alcohol Reaction

In severe reactions, whether caused by an excessive test dose or by the patient's unsupervised ingestion of alcohol, supportive measures to restore blood pressure and treat shock should be instituted. Other recommendations include: oxygen, carbogen (95% oxygen and 5% carbon dioxide), vitamin C intravenously in massive doses (1 g), and ephedrine sulfate. Antihistamines have also been used intravenously. Potassium levels should be monitored, particularly in patients on digitalis, since hypokalemia has been reported.

HOW SUPPLIED

Antabuse® (disulfiram) Tablets are available in the following dosage strength:

250 mg, NDC 0046-0809-81, white-to-off-white, octagonal-shaped, scored, compressed tablet, embossed with a stylized "A" on one side and imprinted with "ANTABUSE" and "250" on the scored reverse side, in bottles of 100 tablets.

Store at room temperature, approximately 25°C.

Dispense in a tight, light-resistant container as defined in the USP

Ayerst Laboratories Inc.

A Wyeth-Ayerst Company

Philadelphia, PA 19101

Cl 5190-2 Revised May 22, 2000